Evaluation of Left Ventricular Hemodynamics with Noninvasive Methods in Cases of Iron Deficiency

Sule Ceylan1*

1 University of Health Sciences, Gaziosmanpasa Training and Research Hospital, Department of Nuclear Medicine, Istanbul, TR

* Corresponding Author: Sule Ceylan E-mail: ceylansule2003@gmail.com

ABSTRACT

Objective: In this study, we aimed to evaluate the effect of iron deficiency on stress ejection fraction by assessing the change in left ventricular ejection fraction during maximum exercise in individuals with iron deficiency.

Material and Methods: In this retrospective study, 212 patients, presenting with atypical chest pain and undergoing exercise gated myocardial perfusion scintigraphy, were included. Of the patients, 171 (80.7%) were female, with an average age of 50 (37-59) years. Patients were categorized into two groups: those with iron deficiency and those without. All patients exercised for a minimum of 6 minutes, reaching at least 85% of their maximum heart rate (220 - age). Hemogram, iron binding capacity, and serum ferritin values were recorded for all participants. In our study, SF less than 100 µg/L and TSAT less than 20% were considered low.

Results: There was no significant difference in age and gender between the groups with and without iron deficiency (p: 0.758, p: 0.658). Echocardiography-calculated ejection fraction values were 66 (55-72). Rest ejection fraction obtained by force gated myocardial perfusion scintigraphy was 64 (52-70), and post-stress ejection fraction was calculated as 58 (50-69). The rate of decrease in post-stress EF compared to rest EF was calculated as 7.40% (7.81-19.12) in all patients. Echo, rest, and post-stress EF values in group 2 were significantly lower than those in group 1 (p: 0.003, 0.028, 0.0005, respectively). The rate of decrease in post-stress EF between the two groups was significantly higher in group 2 (p: 0.0005).

Conclusion: While decreased iron stores and the presence of an iron deficiency state may be well-tolerated during daily activities, maximal exercise can exacerbate the condition if iron deficiency is underlying and undiagnosed. Early diagnosis of iron deficiency, common in society, before the onset of anemia, and prompt treatment are crucial for public health.

Keywords: gated myocardial perfusion scintigraphy, ejection fraction, iron deficiency

INTRODUCTION

A decline in iron intake not only results in the depletion of iron stores within the body but also gives rise to iron deficiency (ID). The complex etiology of iron deficiency encompasses factors such as an escalated demand for iron, diminished absorption from the intestine, and chronic blood loss. Iron, a vital component in the structural makeup of numerous enzymes and biomolecules, plays a pivotal role in various physiological processes within the body. To counteract the loss of iron, intricate mechanisms are in place, with iron being efficiently recycled (1). The body, remarkably resilient, can endure a prolonged period of iron deficiency; however, a critical turning point is reached when iron deficiency progresses to iron deficiency anemia (IDA), marked by the onset of clinical symptoms (2-3).

In the realm of diagnostic imaging, stress gated myocardial perfusion scintigraphy (GMPS) emerges as a powerful noninvasive tool for probing into coronary artery disease (CAD). This method allows clinicians to scrutinize myocardial perfusion during both rest and stress, offering valuable insights into cardiac function. Our retrospective study specifically focuses on individuals with iron deficiency who underwent myocardial perfusion scintigraphy due to atypical chest pain.
While existing literature provides a foundational understanding of the relationship between iron deficiency and cardiovascular health, there remains a gap in comprehending how iron deficiency influences cardiac hemodynamics during exercise. Hence, the primary objective of this study is to address this gap by meticulously comparing rest and post-stress left ventricular ejection fraction (LVEF) values in patients with and without iron deficiency. Through a nuanced exploration of these parameters, we aim to elucidate the nuanced interplay between iron status and cardiac performance during periods of heightened physiological demand, shedding light on potential implications for clinical practice and public health.

**MATERIAL and METHODS**

Our retrospective study, with ethical approval granted by the Gaziosmanpaşa Training and Research Hospital Ethics Committee on 08.06.2022 (approval number 70), focused on 212 patients who underwent stress gated myocardial perfusion scintigraphy (GMPS) due to complaints of atypical chest pain. Among these patients, 171 (80.7%) were women, with an average age of 50 (range: 37-59). The study categorized patients into two groups: those with iron deficiency and those without. Exclusion criteria encompassed male patients aged 45 years and above and female patients aged 55 years and above. Additionally, individuals with menopause, smoking history, hypertension, hyperlipidemia, and diabetes mellitus were excluded. Body mass index values for all patients were within normal limits.

Echocardiography (Echo) was conducted a maximum of 6 weeks before the GMPS examination. Quantitative assessments were executed with GMPS after rest and stress for all 212 patients, revealing no perfusion defects in any participant. Treadmill exercise stress was administered to all patients using the Bruce protocol, with exercise termination based on fatigue. The stress imaging involved intravenous injection of 8-12 mCi Tc-99m-sestamibi, and 24-36 mCi for rest imaging. The Cedars-Sinai Medical Center’s QGS automated analysis program facilitated the evaluation of wall movements and thickness in GMPS (4).

GMPS single-photon emission computed tomography (SPECT) images were acquired from the right anterior oblique to the left posterior oblique using a Mediso-Anyscan-S gamma camera. LVEF (left ventricular ejection fraction) was calculated through transthoracic 2D echocardiography. Synchronization with the electrocardiogram (ECG) during the study for GMPS SPECT allowed the clear determination of end-systolic (ESV) and end-diastolic volumes (EDV) (5), following guidelines (6,7).

Throughout exercise, no patients experienced major side effects such as AV block, significant ST depression (>1 mm) on the ECG, myocardial infarction, atrial fibrillation, convulsive seizures, or hemorrhagic or ischemic cerebrovascular events. The patient cohort had no history of chronic drug use, chronic diseases, known coronary artery disease, or cardiac surgery. Patients with rheumatic heart disease, bundle branch block, and pacemakers were excluded.

The scintigraphy results for patients suspected of coronary artery disease were normal. Exclusions from the study involved patients with chronic kidney failure, chronic liver disease, migraine, other chronic diseases, and those using chronic medications and tobacco.

Hematologic parameters (Hb), iron, iron binding capacity (TSAT), and serum ferritin (SF) values were assessed one week before or after scintigraphy for all patients. In our retrospective study, SF levels below 100 µg/L and TSAT levels below 20% were considered low. No chronic or acute inflammation or febrile diseases were present, and Hb levels exceeded 12 g/dl in all patients, with none diagnosed with anemia. The patient group exclusively exhibited iron deficiency. The Gaziosmanpaşa Training and Research Hospital Ethics Committee reapproved our retrospective study on 08.06.2022, with the assigned number 70.

**Statistics**

SPSS version 21 software was used for statistical analysis. For categorical variables, the number and percentage of cases were given. For continuous variables, it was expressed as median (minimum-maximum). Mann-Witney U test was used for continuous variables that were not normally distributed. Chi-square test was used for categorical variables. p<0.05 was considered statistically significant.

**RESULTS**

The median age of the patients in our study cohort was 50 years (37-59). Patients without iron deficiency (ID) were categorized as Group 1, while those with ID were categorized as Group 2. There was no statistically significant difference in age between the two groups (p: 0.758). Of the 212 patients, 171 (80.7%) were female, and there was no significant gender-based difference between the groups (p: 0.658).

Echocardiography (Echo) calculated ejection fraction (EF) values were 66 (55-72). Rest EF obtained from Gated Myocardial Perfusion Scintigraphy (GMPS) was calculated as 64 (52-70), and post-stress EF was 58 (50-69). The calculated decrease rate of post-stress EF relative to rest EF was 7.40% (7.81-19.12) across all patients.

Notably, 37 patients exhibited High-Density Lipoprotein (HDL) levels above 60 mg/dl, and no significant difference was observed between the two groups in this regard (p: 0.772).

However, when comparing Group 1 and Group 2, Echo, rest, and post-stress EF values were significantly lower in Group 2 (p: 0.003, 0.028, 0.0005, respectively). Moreover, the rate of decrease in post-stress EF between the two groups was notably higher in Group 2 (p: 0.0005). The results are summarized in Table 1.
DISCUSSION

It is acknowledged that certain patients are predisposed to coronary artery disease (CAD) (8). Established risk factors include age ≥45 in male patients, age ≥55 in female patients, early menopause in women, family history, smoking, hypertension, hypercholesterolemia, low HDL, and DM (8). Our study deliberately excluded patients with known CAD and those presenting with risk factors for CAD. Notably, in our country, the prevalence of smoking is considerably high among men aged 35-45. Additionally, iron deficiency is more prevalent in female patients. Consequently, our study exhibits a higher proportion of female participants in both groups. Importantly, there was no statistically significant difference in terms of gender and age between the two groups. The HDL cholesterol level exceeded 40 mg/dl in all our patients. An HDL cholesterol level above 60 mg/dl is acknowledged as a protective factor for CAD (8-9). In our patient cohort, characterized by the absence of CAD risk factors but presenting with chest pain, left ventricular myocardial perfusion was observed to be within normal limits on GMPS imaging.

Beyond established risk factors, various factors are recognized to augment the risk of CAD. Our study did not delve into factors such as lack of physical activity, atherogenic diet, elevated lipoprotein(a), hyperhomocysteinemia, and proinflammatory risk factors. However, despite the absence of these inquiries, exercise GMPS revealed no perfusion deficiencies suggestive of CAD. None of our patients underwent invasive methods or angiography for the evaluation or treatment of CAD.

End-diastolic volume (EDV) denotes the volume of the left ventricle at the end of the maximal diastolic period, while end-systolic volume (ESV) represents the maximum contraction period. Changes in volumes occur as the heart rate increases (10). A study examining the impact of hyperthyroidism on cardiac functions highlighted the development of diastolic dysfunction due to tachycardia (10).

In our patient group, which comprises individuals with iron deficiency (ID), underlying diastolic dysfunction may be implicated in the observed ejection fraction (EF) changes during exertion.

In healthy individuals, exercise leads to an increase in stroke volume, heart rate, and oxygen consumption up to a certain threshold value (11). Reaching 85-90% of the maximum exercise calculated according to age is deemed sufficient to assess blood flow to the heart muscle (12). Our patients attained these levels during the exercise performed for GMPS assessment, affirming the adequacy of the stress protocol. Exercise GMPS imaging emerged as a valuable tool in evaluating left ventricular perfusion and function in our patient cohort (13).

In our study, left ventricular hemodynamics were assessed noninvasively through GMPS. Numerous studies have explored the relationship between GMPS and left ventricular ejection fraction (LVEF) measured by Echo, with published articles contributing to this body of knowledge (14,15). Our study revealed that LVEF values measured with Echo were higher than those measured with GMPS. Importantly, neither MPS nor Echo serves as a definitive ‘reference method’ (16). A study noted that LVEF values measured by MPS were progressively higher in those with elevated LVEF measurements or in older individuals compared to Echo, with lower values in men than in women (17). While Echo is cost-effective and easy to administer, its accuracy may be compromised in patients with ventricular defects (18,19), conditions absent in our study participants.

GMPS assesses left ventricular myocardial perfusion and calculates LVEF. Studies indicate that measurements made with GMPS may be unreliable in the presence of arrhythmia or tachycardia (20). Notably, our patients displayed no arrhythmia during rest electrocardiograms.

Iron is an essential trace element vital for cellular life. Deficiency is prevalent in the population and often remains undetected unless it culminates in anemia.

Table 1: Comparison of left ventricular ejection fractions with non-invasive imaging methods in cases with and without iron deficiency.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (No iron deficiency detected)</th>
<th>Group 2 (Cases with iron deficiency)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50 (37-54)</td>
<td>50 (37-59)</td>
<td>0.758</td>
</tr>
<tr>
<td>Gender(female/male)</td>
<td>90/20 (81.8%)/(18.2%)</td>
<td>81/21 (79.4%)/(20.6%)</td>
<td>0.658</td>
</tr>
<tr>
<td>Echoangiography-Left Ventricular Ejection Fraction Values</td>
<td>66 (55-72)</td>
<td>64.5 (55-72)</td>
<td>0.003</td>
</tr>
<tr>
<td>Gated-myo/perf scintigraphy-rest Ejection Fraction Values</td>
<td>64 (52-70)</td>
<td>63 (53-70)</td>
<td>0.028</td>
</tr>
<tr>
<td>Gated-myo/perf scintigraphy-post-stress Ejection Fraction Values</td>
<td>61 (50-69)</td>
<td>55(50-67)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Percentage difference between post-stress and rest ejection fraction</td>
<td>5.92 (-7.81-9.09)</td>
<td>12.77 (-4.69-19.12)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Percentage of those with High Density Lipoprotein level over 60 mg/dl</td>
<td>20 (18.2%)</td>
<td>17 (16.7%)</td>
<td>0.772</td>
</tr>
</tbody>
</table>
Iron is meticulously regulated within the body, with iron regulatory proteins maintaining cellular iron levels (21). The progression from iron deficiency (ID) to iron deficiency anemia (IDA) is gradual, allowing for the well-tolerance of ID (2). In our study, the discernible decrease in EF with maximal effort was more pronounced in ID patients than in the normal group. This implies that while ID is generally well-tolerated in daily life, it negatively impacts cardiac function during significant exertion, potentially initiating a detrimental cycle. Iron absorption is diminished in patients with chronic heart failure (2), contributing to decreased serum ferritin (SF), transferrin saturation (TSAT), and hemoglobin (Hb) levels (22).

Tissue iron levels are challenging to ascertain, and serum iron levels, fluctuating throughout the day, are not diagnostic. Patients may experience fatigue in the presence of ID (23). In cases with underlying diseases, the presence of ID may exacerbate prognosis. Therefore, early diagnosis and intervention for ID, even before the onset of anemia, hold significance.

Study Limitations:

The weakness of our study is that it is retrospective.

CONCLUSION

While diminished iron stores and the existence of an iron deficiency state are generally well-tolerated in the course of daily activities, our study sheds light on the potential implications of undiagnosed iron deficiency during maximal exercise. The observed exacerbation of cardiac function in individuals with underlying iron deficiency highlights the importance of recognizing and addressing this condition.

Early diagnosis of iron deficiency, particularly in a population where it is prevalent, before it progresses to anemia, emerges as a critical factor in promoting public health. Our findings emphasize the need for increased awareness, timely screening, and intervention strategies to manage iron deficiency effectively. By doing so, we can mitigate the negative impact of iron deficiency on cardiac function, especially during periods of heightened physiological demand, contributing to overall health and well-being.

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Author Contributions: SC: Designed and directed the study, Literature search, Data collection, SC: Article writing, Final revisions. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee. Retrospective study was approved by Gaziosmanpasa Training and Research Hospital Ethics Committee with 70 numbers on 08.06.2022.

Abbreviations:

GMPS: gated myocardial perfusion scintigraphy
SPECT: single photon emission computerized tomography
RF: radiopharmaceutical
BP: Bruce protocol
LVEF: left ventricular ejection fraction
EDV: end-diastolic volume
ESV: end-systolic volume
CAD: coronary artery disease
Echo: echocardiography
ID: Iron Deficiency
Hb: Hemoglobin
SF: serum ferritin
MCV: mean cell volume
MCH: mean cell hemoglobin
RDW: red cell distribution width
TSAT: saturated transferrin
IDA: Iron deficiency anemia
MPS: myocardial perfusion scintigraphy
HDL: High Density Lipoprotein

REFERENCES


